National Stroke Project – Atrial Fibrillation
Clinical Background

According to the American Heart Association, approximately 70 percent of people with atrial fibrillation were between 65 and 85 years of age in 1996. Atrial fibrillation has been estimated to affect between 1.5 and 2.2 million Americans and is the most common sustained cardiac arrhythmia.[1] The incidence of atrial fibrillation increases with age, doubling with each successive decade above 55 years of age. [4]

Atrial fibrillation commonly occurs with rheumatic heart disease, particularly mitral stenosis, and many other cardiac disorders, including coronary heart disease, congestive or hypertrophic cardiomyopathy, mitral valve prolapse, and mitral valve annular calcification. Atrial fibrillation is also very common in conjunction with acute myocardial infarction or following cardiac surgery but usually resolves spontaneously. [2] A number of potentially reversible, noncardiac factors can also cause transient atrial fibrillation including hyperthyroidism, acute alcohol intoxication, cholinergic drugs, noncardiac surgery and diagnostic procedures and pulmonary conditions associated with hypoxemia.[3]

The strongest epidemiological evidence for atrial fibrillation as an independent risk factor for stroke emerged from the Framingham study. [4] The same study defined the risk factors for development of atrial fibrillation. They are, in men, congestive heart failure, age, valve disease, hypertension, diabetes and myocardial infarction (in decreasing value of the odds ratio). These same factors, in the same order, exist for women except for myocardial infarction.[5] While valvular heart disease is a recognized cause of atrial fibrillation, the majority of elderly patients with strokes associated with this arrhythmia have nonvalvular atrial fibrillation.[6] The prevalence of atrial fibrillation in stroke patients increases with age, rising from six percent in patients in the sixth decade to 31 percent in patients in the ninth decade of life. These prevalence data translate to a nearly 25 percent risk of stroke in patients 80 years old and older with atrial fibrillation.[7]

In about 25 percent of elderly people who have atrial fibrillation, the dysrhythmia is intermittent, spontaneously arising and remitting with highly variable frequency, duration and symptoms. [98] Although intermittent atrial fibrillation is common and the tendency to progress from intermittent to permanent atrial fibrillation increases with age, [87] not much is known about the risk of stroke in these patients. A longitudinal cohort study was performed comparing 460 patients in the Stroke Prevention in Atrial Fibrillation (SPAF) studies who had intermittent atrial fibrillation with the 1,552 patients who had sustained atrial fibrillation. Both groups received aspirin and were followed for a mean of two years. Despite a few differences in patient characteristics (those with intermittent atrial fibrillation were younger, more often female and had heart failure less often) the annualized rate of ischemic stroke was similar for those with intermittent (3.2 percent) and sustained (3.3 percent) atrial fibrillation. In the intermittent group, the independent predictors of ischemic stroke were advancing age, hypertension and prior stroke. Of those with intermittent atrial fibrillation considered to be high risk, the stroke rate was 7.8 percent per year. The authors concluded that many elderly patients with intermittent atrial fibrillation would benefit from anticoagulation. [98]

Relevant Therapeutic Interventions

Starting in 1989 and continuing through 1994, the results of six major clinical trials were published, all showing the usefulness of anticoagulation, specifically with warfarin, in reducing the risk of stroke in patients with nonvalvular atrial fibrillation: the Copenhagen AFASAK study, [8] Stroke Prevention in Atrial Fibrillation Study, [9] the Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators, [10] the Canadian Atrial Fibrillation Anticoagulation study, [11] the Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators, [12] the European Atrial Fibrillation Study Group, [13] and the Stroke Prevention in Atrial Fibrillation Investigators [14]. To summarize these studies, the annual rates of embolic stroke in control groups varied from 3.0 percent to 12.3 percent. The annual rate in the warfarin-treated groups varied from 0.41 percent to 3.9 percent. The relative risk reduction varied from 52 percent to 86 percent, and all were statistically significant reductions. A meta-analysis of five of the studies dealing with primary prevention was published in 1994. [15] The annual stroke rate was 4.5 percent in control groups and was 1.4 percent in warfarin groups. This was a risk reduction of 68 percent. Warfarin was efficacious across all subgroups of patients. Aspirin reduced stroke risk by 36 percent. Major hemorrhage was 1.0 percent in control groups, 1.0 percent in aspirin groups and 1.3 percent in warfarin groups. It was recommended that all patients be treated with warfarin except for those under 65 with no other risk factors for stroke (this group is at very low risk for stroke even when not anticoagulated). These findings have appeared in at least 16 reviews published since 1994, all of which concur with the above recommendations. [66-81]

Several meta-analyses published in late 1999 and 2000 support the findings from the published randomized trials related to the use of antithrombotic agents to prevent stroke in patients with atrial fibrillation. [91, 101-104] The authors found that adjusted-dose warfarin significantly reduced the overall relative risk of stroke in patients with and without previous stroke or TIA. In one of these analyses the authors concluded that the occurrence of all strokes is reduced approximately 60 percent by adjusted-dose warfarin compared with no treatment. [91] The efficacy of warfarin for stroke prevention in patients with atrial fibrillation held true when compared to placebo, as well as aspirin. Aspirin was found to modestly reduce stroke in patients with nonvalvular atrial fibrillation. This translates to about ten strokes prevented yearly for every 1000 patients given aspirin for primary prevention. [104] The increased risk for major hemorrhage associated with these agents did not offset this benefit. [91, 101-104]

An observational study in the long-term care setting explored the effect of warfarin as compared to aspirin in reducing the incidence of thromboembolic stroke in older persons with chronic atrial fibrillation. The data showed that compared to aspirin, warfarin administered in a dose to maintain an INR between 2.0 and 3.0 resulted in a 40 percent reduction in thromboembolic stroke in persons with prior stroke and a 31 percent reduction in persons without prior stroke. A similar finding was noted for persons with an abnormal LVEF (45 percent reduction) compared to those with normal LVEF (36 percent). These findings were statistically significant ($p<0.0001$). [89]

Since 1994, several studies have been published evaluating other antiplatelet agents or combinations of fixed, minidose warfarin with aspirin. In a European study, indobufen was only slightly less effective than warfarin in stroke prevention. [16] The patients in this study had recent cerebral ischemic episodes prior to randomization and the stroke rates in control and experimental arm were high. Fixed minidose warfarin with aspirin proved inferior to standard adjusted-dose warfarin in high-risk patients in another trial. [17] The rate of stroke was four times higher in the minidose plus aspirin group and the trial was discontinued after one year. Fixed minidose warfarin

alone is also less efficacious than standard adjustable dose warfarin. [18] These studies confirm what was shown in the original trials: variable dose warfarin at an INR of 2.0 – 3.0 is the best treatment for stroke prevention at this time for patients with nonvalvular atrial fibrillation above the age of 65, with or without other risk factors for stroke.

Based on these findings, consensus statements and/or guidelines were published by the American College of Chest Physicians in 1998,[20,64] the American Heart Association Subcommittee on Electrocardiography and Electrophysiology in 1996,[21] and the American Academy of Neurology in 1998. [65,66] Recently, a review of stroke prevention guidelines and multidisciplinary consensus statement was published by the National Stroke Association with the goal of establishing, in a single resource, up-to-date recommendations for primary care physicians regarding prevention strategies for a first stroke. [22] This consensus statement recommends the use of warfarin for atrial fibrillation in patients greater than 75 years old with or without the presence of risk factors (including age, previous TIA or stroke, hypertension, heart failure, and diabetes mellitus) and in patients 65 to 75 years old with risk factors. In patients 65-75 years old without risk factors, either warfarin or aspirin can be used, and in patients less than 65 years old without risk factors aspirin is recommended. While these guidelines are useful in clinical practice, new prospective studies with many stroke events are needed to more precisely determine the relationship of age to stroke risk with atrial fibrillation and to identify which subgroups carry a sufficiently low stroke risk to forego anticoagulation. [100]

In addition to the four sets of guidelines, the Agency for Healthcare Research and Quality (AHRQ) published an evidence report in May 2000 regarding new onset atrial fibrillation. Recommendations based on an assessment of current scientific evidence cover treatment of underlying conditions as well as control of ventricular rate, cardioversion and prevention of thromboembolism. [93]

Warfarin use

Have these findings resulted in common use of warfarin in clinical practice? Warfarin is underutilized in patients with atrial fibrillation in the acute care setting:

- At six university hospitals, of a cohort of 134 patients with atrial fibrillation and no contraindications to warfarin, 44 percent were discharged on the drug. 25 This same group studied patients with atrial fibrillation admitted for stroke. Even in this setting of tertiary prevention, only 47 percent of the survivors were discharged on warfarin. Also noted was inadequate monitoring of anticoagulation prior to admission. 26
- In a study based at two teaching hospitals and five community hospitals, only 37 percent of eligible patients received warfarin. Increasing risk factors for stroke, including age older than 75 years, were associated with decreased use of warfarin. 27
- In a study of patients with chronic atrial fibrillation of all causes, only 34 percent were treated with warfarin. This analysis showed lower rates in older patients and patients treated in community rather than tertiary care hospitals. [28]
- A study using data from the Cleveland Health Quality Choice database indicated that only 20-21 percent of the high-risk, older patients with atrial fibrillation were receiving anticoagulant therapy. The authors speculated that a high rate of comorbidity and other contraindications were the reason for the low rates of anticoagulant therapy but pointed out that it is precisely this group of high-risk patients that are known to achieve the most benefit from warfarin. [88]

In outpatient settings, warfarin is also underutilized. One interesting study was a follow-up on the patients in the original Canadian (CAFA) trial. They surveyed physicians caring for patients in the trial who continued on therapy after the conclusion of the trial. Of the patients on the warfarin arm, 75 percent continued to take the drug. Of patients on the placebo arm, only 56 percent took the drug after the trial was ended. Two-thirds of the patients not treated with warfarin had refused the therapy. [23] Additionally, in an English general practice, only 36 percent of 111 patients were on warfarin. [24]

There is also room for improvement in the use of warfarin in elderly patients with atrial fibrillation:

- In an academic geriatric practice, 49 percent of high-risk eligible patients were treated with warfarin as recommended by the clinical trials. [29]
- In a study of Medicare beneficiaries at five small Pennsylvania hospitals, 44 percent of 176 eligible patients received warfarin. After implicit review of these cases by an internist and exclusion of additional patients, only 64 percent of the remaining patients had received warfarin. There was also wide variation in the use of warfarin among the five hospitals. [30]
- In a study based in long-term care facilities, the rates were even lower. Only 20 percent of patients without contraindications received warfarin, and less than half of these had PT ratios or INRs in the recommended range. [31]
- In another study in long-term care facilities, 32 percent of 413 patients with atrial fibrillation were treated with warfarin. Many of these patients had contraindications to warfarin use. Also, patients were maintained within the appropriate therapeutic range only 60 percent of the time. [32]
- In the setting of a geriatric rehabilitation hospital, over half the patients were found to have contraindications to warfarin therapy. Of the 35 patients without contraindications, 25 were on warfarin. [33]
- In a primary care practice where elderly patients were screened by electrocardiography, 65 or 5.4 percent of patients had atrial fibrillation. Only 21.4 percent of these were on warfarin, while it was determined that an additional 20 percent were eligible for anticoagulation. [40]

The above studies were all of special or localized populations, and in none were more than a few hundred cases reviewed.

Stafford and Singer examined a more general population using the National Ambulatory Care Surveys from 1980 through 1993: [34]

- Warfarin use in atrial fibrillation increased from 7 percent in 1980 to 32 percent in 1992.
- In 1992-93, warfarin was used in 19 percent of patients 80 years or older, in 39 percent of patients 75-79 years of age, and in 42 percent of patients 65-74 years of age.
- For their patients with atrial fibrillation, cardiologists prescribed warfarin to 40 percent, internists to 32 percent, while general and family practitioners prescribed it to just 15 percent.
- There was no significant difference in warfarin use between male and female patients.
- At 16 percent, warfarin was used less often in the southern United States, compared to 36 percent in the rest of the country.

Brodsky et al conducted a survey in 1996 to determine the attitudes of generalists, specialists and subspecialists regarding the management of atrial fibrillation. Physicians returning the survey

were found to agree on most issues of atrial fibrillation management. One exception was the use of antiarrhythmic drugs. [41]

The Connecticut PRO examined a state-wide cohort of patients hospitalized with atrial fibrillation. They identified 488 patients hospitalized in the first half of 1994, of which 184 patients (38 percent) had relative or absolute contraindications to warfarin use. Among the remaining, only 117 (38 percent) received warfarin. Two-thirds of the untreated patients were also not treated with aspirin. [35] In a related study, they determined that only 53 percent of 278 patients discharged alive with atrial fibrillation and a primary diagnosis of stroke received warfarin. Among ideal candidates, high risk for stroke and low risk for bleeding, only 62 percent received warfarin. [36]

A large Canadian study examined 3,575 patients hospitalized with atrial fibrillation. Among 2,199 patients with nonvalvular atrial fibrillation and no contraindications to anticoagulants, no more than 32 percent were treated with warfarin, and 37 percent received neither aspirin nor warfarin. Elderly and female patients were less likely to be treated. [37]

The Missouri Patient Care Review Foundation (Missouri PRO) has published two studies regarding underuse of antithrombotic therapy:

- In an audit of antithrombotic use in Missouri, rural patients were given antithrombotic therapy less often than urban patients despite a similar high-risk profile and fewer relative contraindications. One reason for this discrepancy was the fact that primary care physicians prescribed antithrombotic therapy less often than cardiologists leading to underutilization in rural areas. [38]
- A more recent study measured the rate of warfarin or aspirin therapy in Medicare patients with NVAF and attempted to link underuse of antithrombotic therapy to adverse outcomes. Overall, 34 percent of patients with NVAF were prescribed warfarin and 21 percent were prescribed aspirin. Advanced age, female gender and rural residency were positively predictive of antithrombotic underuse. After controlling for these factors as well as risk factors for stroke and contraindications to anticoagulation, warfarin therapy was associated with a 24 percent relative reduction in adverse outcomes. [92]

These retrospective observational studies on patients apart from clinical trials share a common theme -- warfarin is underutilized in patients with atrial fibrillation despite the strong evidence of its efficacy in stroke prevention. In few of the studies did the use of warfarin exceed 50 percent. In only one study were more than 75 percent of ideal candidates receiving the drug.

Two recently published prospective observational studies reached similar conclusions:

- Involving four communities in the United States, one study looked at adherence to guidelines in the care of a cohort of persons age 70 years or older with a diagnosis of atrial fibrillation. Subjects were identified by atrial fibrillation on EKG at one or more yearly exams from 1993 to 1995 and were then asked to self-report their use of warfarin in 1995. Warfarin was used by 37 percent of the participants (63/172) who had no preexisting indication for its use. Of the 109 participants not using warfarin, 84 percent (92) had at least one clinical risk factor (aside from age) associated with stroke in patients with atrial fibrillation. [39]
- A two-year prospective study in a general hospital in England attempted to determine whether the trial efficacy of stroke prevention with warfarin translated to effectiveness in clinical practice. Patient characteristics, comorbidity, anticoagulation control, stroke rate and

hemorrhagic complications were compared with pooled data from the randomized trials. Patients were older, included more women and spent significantly less time in the target range than patients in the randomized trials. Of the 167 patients with atrial fibrillation and at high risk for stroke who received long-term warfarin therapy, the INR was in the target range (2.0-3.0) 61 percent of the time, below INR target range 26 percent of the time and above 13 percent of the time. Despite the differences in patient population, the incidence of stroke and major and minor bleeding complications in the study group was comparable to that of patients receiving warfarin in the pooled studies. [99]

Although the clinical trials showed a low risk of complications from anticoagulation, a major fear of warfarin therapy in patients outside clinical trials might be major bleeding, in particular intracranial hemorrhage. Most recent studies on the complications of warfarin therapy in general populations look at patients on warfarin for a variety of indications. Thus, few contain enough patients with atrial fibrillation for meaningful analysis. However, the rate of major bleeding complications in these more general groups was not dissimilar from the complication rates in the clinical trials. [42,43]

The SPAF investigators looked more closely at the bleeding complications in their patients. The risk of major hemorrhage for patients on warfarin was 2.3 percent per year; the risk of intracranial hemorrhage was 0.9 percent per year. Both figures are considerably below the risk for stroke in untreated patients even if the stroke rate in warfarin-treated patients is added. Age, number of prescribed medications and higher INR were risks for hemorrhage. In the warfarin-treated patients, the risk of hemorrhage and intracranial hemorrhage was three-fold higher in patients older than 75 years compared to younger patients.[44] Up to 11 percent of atrial fibrillation patients on warfarin have occult gastrointestinal blood loss. [45] In patients with nonrheumatic atrial fibrillation and stroke with hemiparesis, those treated with warfarin have lower bone mineral density that is probably related to the lower vitamin K concentrations and metabolism in treated patients. [46] While these studies show that anticoagulation is not without risk, the consensus is that benefit of stroke prevention outweighs the risk even in the non-trial setting. Inadequate anticoagulation also increases the risk of stroke in patients with atrial fibrillation. At INRs below 2, the risk for stroke increases: stroke risk of 2.0 at INR 1.7, stroke risk of 3.3 at INR 1.5 and stroke risk of 6.0 at INR 1.3. [47]

In April 2000 the Japanese Nonvalvular Atrial Fibrillation – Embolism Secondary Prevention Cooperative Study Group published results regarding optimal intensity of warfarin therapy. [90] This prospective, multicenter, randomized trial compared the efficacy and safety of conventional (INR 2.2 to 3.5) to low-intensity (INR 1.5 to 2.1) warfarin in patients < 80 years of age. All patients had a definite (or possible) cardioembolic stroke or TIA due to non-valvular atrial fibrillation (NVAF) one to six months prior to entry into the trial. This trial was prematurely halted after a follow-up of less than two years due to major hemorrhagic complications in six patients in the conventional therapy group. All of the patients with hemorrhage were elderly (mean age 74 years) and their mean INR was 2.8. The authors concluded that for secondary prevention of stroke in persons with atrial fibrillation, low-intensity warfarin treatment is safer than conventional-intensity. There are several caveats to note when comparing these results to others: 1) this study involved only 115 patients; 2) the upper range of the conventional intensity INR was higher than that recommended in the United States; and 3) the difference in diet and culture between this Japanese patient

population and a similar one in the United States may have a significant effect on warfarin metabolism. [90]

While silent cerebral infarction is a risk in patients with atrial fibrillation, there are no recently published studies with sufficient numbers of patients to suggest that anticoagulation would protect against it.

Physician Attitudes

Several studies have explored physician attitudes toward warfarin use in NVAF:

- In a British study, warfarin use for atrial fibrillation associated with dilated cardiomyopathy would have been prescribed by 52 percent of geriatricians and 86 percent of cardiologists. The figures for lone atrial fibrillation were 10 percent of geriatricians and 26 percent of cardiologists. Nearly 90 percent of both groups would prescribe warfarin for atrial fibrillation in association with mitral stenosis. [48]
- Only 20 percent of British general practitioners would consider prescribing warfarin for patients with atrial fibrillation who had a recent TIA or minor stroke. [49]
- In an American study from two university and five community hospitals, the 80 surveyed physicians recommended warfarin less often for older patients, for those with bleeding risks, and for those patients who had not experienced stroke. The physicians also reported that they prescribed warfarin for less than half their patients for whom warfarin was thought appropriate by an independent reviewer knowledgeable about the recommendations from recent clinical trials. [50]
- A survey of physicians caring for nursing home patients in New England, Quebec and Ontario showed only 47 percent felt that the benefits of warfarin greatly outweighed the risks in these patients with atrial fibrillation. [51]
- In a survey from Alberta, Canada, 92 percent of internists and cardiologists would prescribe warfarin for elderly patients with atrial fibrillation and stroke risk compared to 76 percent of general practitioners. [52]
- In a study of a subgroup of participants in the Cardiovascular Health Study, investigators found that despite widely publicized practice guidelines, only 23-50 percent of the participants with atrial fibrillation were treated with warfarin. [39] Of those patients not being treated with warfarin, 84 to 90 percent were elderly and had at least one other risk factor for stroke.
- A Canadian article explored the issue of physician reluctance to prescribe warfarin to elderly patients they deem at risk for falls through the use of a decision analytic model. The authors' concluded that, while there are many clinical factors associated with the choice of optimal antithrombotic therapy for elderly patients with atrial fibrillation, the patient's propensity for falling was not an important factor. [53]

While survey results are dependent on response rates and questions asked (or clinical vignettes presented), the studies summarized above show there is a variation and some reluctance on the part of physicians to prescribe warfarin to the extent recommended based on results of recent clinical trials.

In addition to underuse of warfarin, there is growing evidence that physicians in primary care practice do not experience the same outcomes as those achieved in the randomized trials. [97] Patient-related barriers include age, perceived embolic risk and perceived risk of hemorrhage. The physician’s perception of the benefit versus the risk of therapy is the only consistent finding

influencing the implementation of warfarin therapy. According to the authors, this perception is likely derived from previous experience with the use of warfarin. One survey reported that 79 percent of physicians cited a lack of patient reliability as a contraindication to warfarin therapy and greater than 90 percent of the same group did not prescribe warfarin to patients with a history of alcoholism. [97] Two additional barriers related to less than optimal anticoagulation management have been identified: 1) laboratory test results may not be available until after the patient has left the clinic, thus complicating the process of dosage adjustment; and 2) inadequate record-keeping can lead to dosage changes being communicated to patients late or not at all and to delays in rescheduling missed appointment. [94,95]

Patient Attitudes

Two recent studies used decision analytic techniques to study patients' preferences and attitudes toward anticoagulation as stroke prophylaxis. Both studies interviewed patients with NVAF:

- In one study, patients indicated a preference for warfarin therapy if it reduced their risk for stroke by 20 percent in the following two years. [54]
- In another study, the striking findings related to the wide variation in the importance placed on the risk for severe stroke and the value of warfarin therapy. This variation was so great that the authors concluded that patients' preferences must be taken into account when choosing therapy for stroke prophylaxis. In older patents or patients with no risk factors for stroke, there was a tendency for aspirin to be the preferred therapy rather than warfarin because of the low utility some patients placed on the use of warfarin. [55]

Cost-effectiveness

Several studies used decision-analytic techniques to determine the cost-effectiveness of anticoagulation prophylaxis in patients with nonvalvular atrial fibrillation. Prescribing warfarin for a 65 year-old with one additional risk factor for stroke costs $8,000 per quality-of-life-year (QALY) saved. This rises to $110,000 if the patient is 75 years old or older. If the patient 65 years old with no risk factors, the cost is $370,000. [56]

These same authors, in a follow-up study, incorporated patient preference into the outcome of the decision analysis, based on their work cited above. It showed that aspirin was equivalent to warfarin in patients at higher risk for stroke, but as the risk of stroke decreased, there was increasing advantage to using aspirin in cases where patients indicated low utility for warfarin therapy compared to aspirin. [57]

The decision analysis studies cited above support the clinical trials, in general, as they must, considering that their probabilities were based on them. However, base cases and utilities vary from study to study, making it difficult to apply their findings to broad-based epidemiological studies aimed at quality improvement. As a limited generalization, one could conclude that they do not contradict the need for increased use of warfarin (in fact they show warfarin to be quite cost-effective in many situations), but do point out individual scenarios where aspirin or cardioversion with maintained normal sinus rhythm might be the preferred choice.

Patient education regarding warfarin/planned prothrombin time

A recent study designed to test the lowest effective level of prophylactic anticoagulation found that among patients with atrial fibrillation, INRs of 2.0 or greater are effective.[47] Because the risk of hemorrhage rises rapidly at INRs greater than 4.0 to 5.0, the role of tight control of anticoagulant

therapy to maintain the INRs between 2.0 and 3.0 is clear. This role is especially important in the more elderly patient because consistent prothrombin times are difficult to maintain due to erratic food intake, instability of coexisting illness, multiple medications and confusing regimens. [61] Education regarding warfarin dosing, dietary intake of vitamin K, the use of alcohol, common drug interactions, avoidance of falls, and the importance of regular prothrombin level checks should be a basic part of discharge planning for these patients. In addition, an appointment for a prothrombin level check should be made prior to discharge.

Thyroid Testing

Hyperthyroidism should always be considered for patients when atrial fibrillation occurs without apparent cardiac origin, especially if the ventricular response is rapid. [44, 86]

In older patients with diagnosed hyperthyroidism, atrial fibrillation is a common clinical finding:

- In 60 patients 70 years old and older with hyperthyroidism, and with low thyrotropin level (TSH) as one of the criteria, 60 percent (36 of 60) were in atrial fibrillation. [82]
- In patients with subclinical thyrotoxicosis, defined as low TSH with normal free thyroxine (T_4) level, 28 percent (11 of 40) were in atrial fibrillation, compared to ten percent (four of 40) in a euthyroid group. These patients had an average age of 65 years. [83]
- In patients with congestive heart failure, 12 percent developed atrial fibrillation (28 of 344) and had consistently lower levels of TSH during a follow-up period of 19 months, 1.6 mU/L vs 2.2 mU/L for those who remained in sinus rhythm. [84] This difference was not statistically significant.

Data from a study by Sawin et al, [85] showed that low TSH is a risk factor for development of atrial fibrillation. This study followed 2,007 patients 60 years old or older who were initially in sinus rhythm. After ten years, follow-up was performed for the cohort. Of the 2,007 patients, 192 developed atrial fibrillation. The relative risk of developing atrial fibrillation for patients with low TSH was 3.1 percent (3.8 percent if patients being treated for hyperthyroidism were excluded).

Most physicians who care for these patients favor routine testing for thyroid function for elderly patients with atrial fibrillation. In a survey of 904 physicians, more than 90 percent indicated they would order such tests, with no significant difference noted among the three types of physicians (internists, cardiologists and electrophysiologists). [41]

Echocardiograms

Valvular heart disease is a well-documented cause of atrial fibrillation. In addition, valvular heart disease in combination with atrial fibrillation increases the risk for thromboembolism and stroke. Patients with valvular disease and an atrial thrombus may require more intensive antithrombotic therapy and closer monitoring.[21] Occasionally, surgical valve replacement may be needed to stabilize cardiac function. The performance of echocardiography permits the identification of valvular disease and may detect an atrial thrombus. If these high risk patients are promptly identified, physicians can approach them with the necessary higher level of care.

The use of transesophageal echocardiography in the management of patients with atrial fibrillation continues to evolve. There is promise that high-risk patients may be identified by echocardiographic findings, especially important for evaluation of cardiogenic thrombotic risk in patients for whom electrical cardioversion is planned. [62,63] However at present it seems that

routine use of transesophageal echocardiography is not warranted as many patients will benefit from empirical anticoagulation therapy.

According to the AHRQ evidence report regarding new onset atrial fibrillation published in May 2000, there are no completed trials that directly address the clinical utility of echocardiography in the management of atrial fibrillation. However, using decision analysis processes, both transthoracic (in patients without risk factors for thromboembolism) and transesophageal (in patients with risk factors for thromboembolism) echocardiography were projected to be a cost-effective test for guiding decisions about the choice of antithrombotic treatment in most patients. [93]

Changing Clinical Processes

A quality improvement study conducted by a community teaching hospital in Boston began with the identification of an opportunity for improvement regarding warfarin therapy for patients with atrial fibrillation. [96] Through a retrospective chart audit, the hospital discovered that only 45 percent of eligible patients with atrial fibrillation were prescribed warfarin at discharge. In addition, an analysis of admission INRs indicated that only a minority were safely anticoagulated. An anticoagulation clinic was established in fall 1997 and in early 1998 monitoring of patients with atrial fibrillation began. Remeasurement showed that the proportion of patients receiving warfarin increased from 46 percent in February-May 1998 to 63 percent in April-June 1999. The proportion of INRs in the desired range increased from 49 percent to 54 percent.

Bibliography

1. Anderson DC et al. Preliminary report of the stroke prevention in atrial fibrillation study. *N Eng J Med;*. March 22, 1990, 322 (12): 863-868.

2. Ommen SR, Odell JA and Stanton MS. Atrial arrhythmias after cardiothoracic surgery. *N Eng J Med*; May 15, 1997; 336(20):1429-34.

3. Alberts MJ, Dawson DV, Massey EW. A follow-up survey of clinical practices for the use of heparin, warfarin, and aspirin. *Neurology*. 1994 April 44(4): 618-21.

4. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke. The Framingham Study. *Stroke*; Aug 1991;22(8):983-8.

5. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA*; Mar 16, 1994;271(11):840-4.

6. Fisher CM. Reducing risks of cerebral embolism. *Geriatrics;* Feb 1979;34(12):59-61.

7. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. *Arch Intern Med*; Sep 1987;147(9):1561-4.

8. Peterson P, Boysen G, Godtfredsen J et al. Placebo-controlled randomized trial of warfarin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASAK study. *Lancet*; Jan 28, 1989;I(8631):175-9.

9. Stroke Prevention in Atrial Fibrillation Investigators. Stroke Prevention in Atrial Fibrillation Study. Final Results. *Circulation;* Aug 1991;84(2):527-39.

10. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med*; Nov 29, 1990;323(22):1505-11.

11. Connolly SJ, Laupacis A, Gent M, et al. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. *J Am Coll Cardiol*; Aug 1991; 18(2):349-55.

12. Ezekowitz MD, Bridgers SL, James KE et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. *N Engl J Med*; Nov 12, 1992; 327(20):1406-12.

13. EAFT (European Atrial Fibrillation Study Group). Secondary prevention in non-rheumatic atrial fibrillation after minor transient ischemic attack or minor stroke. *Lancet*; Nov 20, 1993; 342(8882): 1255-62.

14. Stroke Prevention in Atrial Fibrillation Investigators. Warfarin versus aspirin for the prevention of thromboembolism in atrial fibrillation. The stroke prevention in atrial fibrillation II study. *Lancet*; Mar 19, 1994;343(8899):687-91.

15. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from 5 randomized controlled trials. *Arch Intern Med*; Jul 11, 1994;154(13):1449-57.

16. Morocutti C, Amabile G, Fattapposta F et al. Indobufen versus warfarin in the secondary prevention of major vascular events in nonrheumatic atrial fibrillation. SIFA investigators. *Stroke*; May 1997; 28(5):1015-21.

17. SPAF investigators. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomized clinical trial. *Lancet;* Sep 7, 1996;348(9028):633-8.

18. Pengo V, Zasso A, Barbero F et al. Effectiveness of fixed minidose warfarin in the prevention of thromboembolism and vascular death in nonrheumatic atrial fibrillation. *Am J Cardiol*; Aug 15, 1998;82(4):433-7.

19. Gottlieb LK, Salem-Schatz S. Anticoagulation in atrial fibrillation. Does efficacy in clinical trials translate into effectiveness in practice? *Arch Intern Med*; Sep 12, 1994; 154(17):1945-53.

20. Laupacis A et al. Antithrombotic therapy in atrial fibrillation. *Chest*; Nov 1998; 114(5 Suppl):579S-589S.

21. Prystowsky EN et al. Management of patients with atrial fibrillation. *Circulation*; Mar 15, 1996; 93(6):1262-77.

22. Gorelick PB et al. Prevention of first stroke: a review of guidelines and a multidisciplinary consensus statement from the National Stroke Association. *JAMA*; March 24/31, 1999; 281(12):1112-1120.

23. Laupacis A, Sullivan K. Canadian atrial fibrillation anticoagulation study: were the patients subsequently treated with warfarin? Canadian Atrial Fibrillation Anticoagulation Study Group. *Can Med Assoc J;* June 1, 1996; 154(11):1669-74.

24. Lip GY, Golding DJ, Nazir M et al. A survey of atrial fibrillation in general practice: the West Birmingham Atrial Fibrillation Project. *Br J Gen Pract*; May 1, 1997;47(418):285-9.
25. Albers GW, Yim JM, Belew KM et al. Status of antithrombotic therapy for patients with atrial fibrillation in university hospitals. *Arch Intern Med;* Nov 11, 1996;156(20):2311-6.

26. Albers GW, Bittar N, Young L et al. Clinical characteristics and management of acute stroke in patients with atrial fibrillation admitted to US university hospitals. *Neurology;* Jun 1997; 48(6):1598-604.

27. Antani MR, Beyth RJ, Covinsky KE. Failure to prescribe warfarin to patients with nonrheumatic atrial fibrillation. *J Gen Intern Med;* Dec 1996;11(12):713-20.

28. Munschauer FE, Priore RL, Hens M et al. Thromboembolism prophylaxis in chronic atrial fibrillation. Practice patterns in community and tertiary-care hospitals. *Stroke;* Jan 1997;28(1):72-6.

29. Mendelson G, Aronow WS. Underutilization of warfarin in older persons with chronic nonvalvular atrial fibrillation at high risk for developing stroke. *J Am Geriatr Soc*; Nov 1998; 46(11):1423-4.

30. Whittle J, Wickenheiser L, Venditti LN. Is warfarin underused in the treatment of elderly persons with atrial fibrillation? *Arch Intern Med*; Feb 24, 1997;157(4):441-5.

31. Lackner TE, Battis GN. Use of warfarin for nonvalvular atrial fibrillation in nursing home patients. *Arch Fam Med;* Dec 1995;4(12):1017-26.

32. Gurwitz JH, Monette J, Rochon PA et al. Atrial fibrillation and stroke prevention with warfarin in the long-term care setting. *Arch Intern Med;* May 12, 1997; 157(9):978-84.

33. Lawson F, McAlister F, Ackman M et al. The utilization of antithrombotic prophylaxis in a geriatric rehabilitation hospital. *J Am Geriatr Soc;* Jun 1996;44(6):708-11.

34. Stafford RS, Singer DE. National patterns of warfarin use in atrial fibrillation. *Arch Intern Med*; Dec 9-23, 1996;156(22):2537-41.

35. Brass LM, Krumholz HM, Scinto JM, Radford M. Warfarin use among patients with atrial fibrillation. *Stroke*; Dec 1997;28(12):2382-9.

36. Brass LM, Krumholz HM, Scinto JM, Radford M. Warfarin use following ischemic stroke among Medicare patients with atrial fibrillation. *Arch Intern Med;* Oct 26, 1998;158(19):2093-100.

37. The Clinical Quality Improvement Investigators. Thromboembolic prophylaxis in 3575 hospitalized patients with atrial fibrillation. *Can J Cardiol*; May 1998;14(5): 695-702.

38. Flaker GC et al. Underutilization of antithrombotic therapy in elderly rural patients with atrial fibrillation. *Am Heart J*; Feb 1999; 137(2):307-12.

39. White RH et al. Oral anticoagulation in patients with atrial fibrillation: adherence with guidelines in an elderly cohort. *Am J Med*; Feb 1999; 106(2):165-71.

40. Wheeldon NM, Tayler DI, Anagnostou E et al. Screening for atrial fibrillation in primary care. *Heart;* Jan 1998;79(1):50-5.

41. Brodsky et al. Regional attitudes of generalists, specialists and subspecialists about management of atrial fibrillation. *Arch Intern Med*; Dec 9-23 1996; 156:2553-62.

42. McKenna CJ, Galvin J, McCann HA, Sugrue DD. Risk of long-term anticoagulation in a non-trial medical environment. *Ir Med J;* Jul-Aug 1996;89:144-5.

43. Dahl T, Abildgaard U, Sandset PM. Long-term anticoagulant therapy in cerebrovascular disease: does bleeding outweigh the benefit? *J Intern Med*; Mar 1995;237(3):323-9.

44. The Stroke Prevention in Atrial Fibrillation Investigators. Bleeding during antithrombotic therapy in patients with atrial fibrillation. *Arch Intern Med*; Feb 26, 1996;156(4):409-16.

45. Blackshear JL, Baker VS, Holland A et al. Fecal hemoglobin excretion in elderly patients with atrial fibrillation: combined aspirin and low-dose warfarin vs conventional warfarin therapy. *Arch Intern Med*; Mar 26, 1996;156(60:658-60.

46. Sata Y, Honda Y, Kunoh H, Oizumi K. Long-term oral anticoagulation reduces bone mass in patients with previous hemispheric infarction and nonrheumatic atrial fibrillation. *Stroke*; Dec 1997;28(12):2390-4.

47. Hylek EM, Skatews SJ, Sheehan MA, Singer DE. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. *N Engl J Med*; Aug 22, 1996;335(8):540-6.

48. King D, Davies KN, Slee A, Silas JH. Atrial fibrillation in the elderly: physician attitudes to anticoagulation. *Br J Clin Pract*; May-Jun 1995;49(3):123-5.

49. Mead GE, Murray H, McCollum CN, O'Neill PA. How do general practitioners manage patients at risk from stroke? *Br J Clin Pract*; Dec 1996;50(8):426-30.

50. Beyth RJ, Antani MR, Covinsky KE et al. Why isn't warfarin prescribed to patients with nonrheumatic atrial fibrillation? *J Gen Intern Med;* Dec 1996;11(12):721-8.

51. Monette J, Gurwitz JH, Rochon PA, Avorn J. Physician attitudes concerning warfarin for stroke prevention in atrial fibrillation: results of a survey of long-term care practitioners. *J Am Geriatr Soc*; Sep 1997;45(9):1060-5.

52. Kellen JC, Russell ML. Physician specialty is associated with differences in warfarin use for atrial fibrillation. *Can J Cardiol*; Mar 1998;14(3):365-8.

53. Man-Son-Ling M, Nichol G, Lau A, Laupacis A. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. *Arch Intern Med*; Apr 12, 1999; 159(7):677-85.

54. Man-Son-Ling M, Laupacis A, O'Conner A et al. Warfarin for atrial fibrillation. The patient's perspective. *Arch Intern Med*; Sep 9, 1996;156(16):1841-8.

55. Gage BF, Cardinalli AB, Owens DK. The effect of stroke and stroke prophylaxis with aspirin or warfarin on quality of life. *Arch Intern Med*; Sep 6, 1996;156(16):1829-36.

56. Gage BF, Cardinelli AB, Albers GW, Owens DK. Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation. *JAMA*; Dec 20, 1995; 274(23):1839-45.

57. Gage BF, Cardinalli AB, Owens DK. Cost-effectiveness of preference-based antithrombotic therapy for patients with nonvalvular atrial fibrillation. *Stroke*; Jun 1998;29(6):1083-91.

58. Middlekauff HR, Stevenson WG, Gorbein JA. Antiarrhythmic prophylaxis vs warfarin anticoagulation to prevent thromboembolic events among patients with atrial fibrillation. A decision analysis. *Arch Intern Med*; May 8, 1995;155(9):913-20.

59. Disch DL, Greenberg ML, Holzberger PT et al. Managing chronic atrial fibrillation: A Markov decision analysis comparing warfarin, quinidine, and low-dose amiodarone. *Ann Intern Med*; Mar 15, 1994;120(6):449-57.

60. Eckman MH, Falk RH, Pauker SG. Cost-effectiveness of therapies for patients with nonvalvular atrial fibrillation. *Arch Intern Med*; Aug 10-24, 1998; 158(15):1669-77.

61. Fong LN. Balancing anticoagulant therapy. *Geriatric Nursing.* 1991 Jan-Feb; 12(1):15-7.

62. Grimm RA, et al. Should all patients undergo transesophageal echocardiography before electrical cardioversion of atrial fibrillation?; *J Am Coll Cardio;* Feb 1994, 23(2):533-541.

63. Cohen IS, Ezekowitz MD. Prevention of thromboembolism in patients with atrial fibrillation. *Cardio Clinics*; Nov 1996; 14(4):537-42.

64. Albers GW et al. Antithrombotic and thrombolytic therapy for ischemic stroke. *Chest*; Nov 1998; 114(5Suppl):683S-698S.

65. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: stroke prevention in patients with nonvalvular atrial fibrillation. *Neurology*; Sep 1998; 51(3):671-73.

66. Hart RG et al. Prevention of stroke in patients with nonvalvular atrial fibrillation. *Neurology*; Sep 1998 51(3):674-81.

67. Gallus AS. Towards the safer use of warfarin I: an overview. *J Qual Clin Pract*; Mar 1999; 19(1): 55-9.

68. Nademannee K, et al. Long-term antithrombotic treatment for atrial fibrillation. *Am J Cardiol*; Oct 16, 1998: 82(8A):37N-42N.

69. Chandramouli BV, et al. Atrial fibrillation: preventing thromboembolism and choosing nondrug therapies. *Geriatrics*; Jul 1998; 53(7):53-60.

70. Akhtar W, et al. Indications for anticoagulation in atrial fibrillation. *Am Fam Phy*; Jul 1998; 58(1):130-6.

71. Chrzanowski DD. Managing atrial fibrillation to prevent its major complication: ischemic stroke. *Nurse Pract*; May 1998; 23(5):26, 32-7, 41-2.

72. Wolf PA, et al. Preventing stroke in atrial fibrillation. *Am Fam Phy*; Dec 1997; 56(9):2242-50.

73. Gershlick AH. Treating the non-electrical risks of atrial fibrillation. *Eur Heart J*; May 1997; 18(Suppl C):C19-26.

74. Ackermann RJ. Anticoagulant therapy in patients aged 80 years or more with atrial fibrillation: more caution is needed. *Arch Fam Med*; Mar-Apr 1997; 6)2):105-10.

75. Blackshear JL, et al. Management of atrial fibrillation in adults: prevention of thromboembolism and symptomatic treatment. *Mayo Clin Proc*; Feb 1996; 71(2):150-60.

76. Morley J, et al. Atrial fibrillation, anticoagulation, and stroke. *Am J Cardiol*; Jan 25, 1996; 77(3): 38A-44A.

77. Gottlieb LK, et al. Anticoagulation in atrial fibrillation: does efficacy in clinical trials translate into effectiveness in practice? *Arch Intern Med*; Sep 12, 1994; 154(17):1945-53.

78. Dalen JE. Atrial fibrillation: reducing stroke risk with low-dose anticoagulation. *Geriatrics*; May 1994; 49(5):24-6, 29-32.

79. Nelson KM, et al. Preventing stroke in patients with nonrheumatic atrial fibrillation. *Am J Hosp Pharm*; May 1, 1994; 51(9):1175-83.

80. Golden WE, et al. Arkansas Foundation for Medical Care report: preventing stroke in atrial fibrillation. *J Ark Med Soc*; Feb 1994; 90(9):439-40.

81. Hart RG. Prevention of stroke in atrial fibrillation: an update. *Health Rep*; 1994; 6(1):126-31.

82. Martin FI, Deam DR. Hyperthyroidism in elderly hospitalized patients:clinical features and treatment outcomes. *Med J Aust*; Feb 19,1996; 164(4):200-203.

83. Tenerez A, Forberg R, Jansson R. Is a more active attitude warranted in patients with subclinical thyrotoxicosis? *J Intern Med*; Sep 1990; 228(3):229-33.

84. Pozzoli M et al. Predictors of primary atrial fibrillation and concomitant clinical and hemodynamic changes in patients with chronic congestive heart failure: a prospective study in 344 patients with baseline sinus rhythm. *J Am Coll Cardio*; Jul 1998; 32(1):197-204

85. Sawin CT, Geller A, Wolf PA. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older patients. *N Engl J Med*; 1994; 331:1249-52.

86. *Harrison's Principles of Internal Medicine*; Fauci AS et al, Editors; McGraw Hill; 1998; pg. 1264.

87. Al-Khatib SM et al. Observations on the transition from intermittant to permanent atrial fibrillation. *Am Heart J* July 2000;140(1):142-45.

88. Ibrahim SA et al. Underutilization of oral anticoagulant therapy for stroke prevention in elderly patients with heart failure. *Am Heart J* 2000;140(2):219-20.

89. Aronow WS et al. Effect of warfarin versus aspirin on the incidence of new thromboembolic stroke in older persons with chronic atrial fibrillation and abnormal and normal left ventricular ejection fraction. *Am J Cardio* Apr 15, 2000;85(8):1033-35.

90. Yamaguchi T. Optimal intensity of warfarin therapy for secondary prevention of stroke in patients with nonvalvular atrial fibrillation: a multicenter, prospective, randomized trial, Japanese Nonvalvular Atrial Fibrillation – Embolism Secondary Prevention Cooperative Study Group. *Stroke* Apr 2000;31(4):817-21.

91. Hart RG et al. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Int Med* 1999:131:492-501.

92. Gage BF et al. Adverse outcomes and predictors of underuse of antithrombotic therapy in Medicare beneficiaries with chronic atrial fibrillation. *Stroke* Apr 2000:31:822-27.

93. Agency for Healthcare Research and Quality. *Evidence Report/Technology Assessment:Number 12*. Management of new onset atrial fibrillation summary. May 2000;1-12.

94. Ansell JE. The quality of anticoagulation management. *Arch Int Med* Apr 10, 2000;160(7):1-5.

95. Samsa GP et al. Quality of anticoagulation management among patients with atrial fibrillation: results of a review of medical records from two communities. *Arch Int Med* Apr 10, 2000;160(7):967-73.

96. Gaughan GL et al. Improving management of atrial fibrillation and anticoagulation in a community hospital. *Jnt Comm J Qual Improv* Jan 2000;26(1):18-28.

97. Bungard TJ et al. Why do patients with atrial fibrillation not receive warfarin? *Arch Int Med* Jan 10, 2000; 160(1):41-6.

98. Hart RG et al. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke Prevention in Atrial Fibrillation Investigators. *J Am Coll Cardio* Jan 2000;35(1):183-7.

99. Kalra et al. Prospective cohort study to determine if trial efficacy of anticoagulation for stroke prevention in atrial fibrillation translates into clinical effectiveness. *BMJ* May 6, 2000;320:1236-9.

100. Go AS et al. Implication of stroke risk criteria on the anticoagulation decision in nonvalvular atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Circ* Jul 4, 2000;102(1):11-13.

101. Koudstaal PJ. Anticoagulants versus antiplatelet therapy for preventing stroke in patients with nonrheumatic atrial fibrillation and a history of stroke or transient ischemic attacks. *Cochrane Database Syst Rev* 2000;(2):CD000187.

102. Koudstaal PJ. Antiplatelet therapy for preventing stroke in patients with nonrheumatic atrial fibrillation and a history of stroke or transient ischemic attacks. *Cochrane Database Syst Rev* 2000;(2):CD000186.

103. Benavente O et al. Antiplatelet therapy for preventing stroke in patients with nonvalvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *Cochrane Database Syst Rev* 2000;(2):CD001925.

104. Benavente O et al. Oral anticoagulants for preventing stroke in patients with nonvalvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *Cochrane Database Syst Rev* 2000;(2):CD001927.